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REMARKS

Applicants respectfully request formal examination of this application.

I. Summary of the Amendments to the Claims

Claims 1-22, 25-29, 37-44, 53, and 54 have been amended to clarify that the claims are limited to solid dosage forms. This is consistent with the scope of the pending method claims. In addition, claims 1, 30, and 35 have been amended to clarify that by "an effective average particle size of less than about 1000 nm," it is meant that at least 50% of the active agent particles have a size of less than 1000 nm. Finally, claim 14 has been amended to note that solid dosage forms of the invention include powders.

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Summary of the Claimed Invention

The claimed invention is directed to the surprising discovery of controlled release nanoparticulate active agent compositions, methods of preparing such compositions, and methods of treating mammals using such compositions.

The controlled release compositions provide for the therapeutically effective release of an incorporated nanoparticulate active agent in a patient for a time period ranging from about 2 to about 24 hours. This discovery was surprising because nanoparticulate active agent compositions are designed for immediate, fast release. Such fast release results from the nanoparticulate size of the active agent, having a large surface area in relation to the volume, which results in rapid dissolution of the active agent following administration. However, rapid dissolution is contrary to the goal of controlled release formulations.

Applicants unexpectedly discovered that nanoparticulate active agent compositions could be effectively formulated into controlled release compositions by incorporating a rate controlling polymer in either a matrix with the nanoparticulate active agent composition, or in a film coating the nanoparticulate active agent composition. This is not shown or suggested by the cited prior art.

III. Summary of the Advisory Action

A. Rejection of the Claims Over Liversidge

In the Advisory Action mailed on August 13, 2003, the Examiner maintained the rejection of claims 1-22 and 25-53 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,145,684 ("Liversidge"). In support of maintaining the rejection, the Examiner stated that:

> Applicant's arguments center around a comparison of an immediate release dosage form with a controlled release dosage form. However, there has still been no evidence provided that the formulation of Liversidge does not have a release rate which falls within the release rate claimed by applicant.

Applicants respectfully traverse this ground for rejection.

1. The Jain Declaration Demonstrates that Solid Dose Forms of the Nanoparticulate Dispersions of Liversidge do not Exhibit Inherent Controlled Release Properties

As described in more detail in the accompanying Declaration of Rajeev A. Jain ("the Jain Declaration"), by design the nanoparticulate drug compositions of Liversidge allow for rapid dissolution and, therefore, rapid onset of drug action. Solid dose forms of nanoparticulate active agent dispersions disclosed by Liversidge will not exhibit controlled release of the component active agent such that release of the active agent extends for about 2 up to about 24 hours, as required by Applicant's claims. *See* ¶ 6 of the Jain Declaration.

This is because solid dose controlled release compositions according to the invention require: (1) a nanoparticulate active agent in combination with a surface stabilizer, **and** (2) a rate controlling polymer present in a matrix around the nanoparticulate active agent particles or in a film coating the composition. This additional component is not taught or suggested by Liversidge. Moreover, given the rapid release of the nanoparticulate active agents of Liversidge, it was not expected that controlled release formulations of such compositions could be made. *See* ¶ 7 of the Jain Declaration.

The Jain Declaration presents data which exemplifies the rapid dissolution of solid dose compositions made according to Liversidge, in contrast to the controlled release compositions of the claimed invention. *See* ¶ 8 of the Jain Declaration.

The compositions described in the examples of Liversidge are liquid dispersions of: (1) danazol and polyvinylpyrrolidone (PVP) (Examples 1-5); (2) steroid A and lecithin (Examples 6 and 14); (3) steroid A and Triton® X-200 (an alkyl aryl polyether sulfonate) (Example 7); (4) steroid A and gum acacia (Example 8); (5) steroid A and sodium lauryl sulfate (SLS) (Example 9); (6) steroid A and docusate sodium (DOSS) (Example 10); and (7) steroid A and Pluronic® F68 (a block copolymer of ethylene oxide and propylene oxide) (Examples 11, 12, and 14). *See* ¶ 9 of the Jain Declaration.

Applicants were not able to readily form solid dosage forms of the nanoparticulate Steroid A dispersions described in the examples of Liversidge. Steroid A, also known as 5β,17β,-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17- ol, is also dangerous to spray dry or spray granulate, is highly potent, which makes the compound extremely difficult to spray dry or spray granulate, processes which are utilized in the formation of a solid dosage form, due to the risk of inhalation. *See* ¶ 10 of the Jain Declaration.

The data and dissolution experiments described in the Jain Declaration reference six active agents: Danazol, Compound A (a leukotrine inhibitor), Compound B (a kinase inhibitor), Compound C (an antiviral agent), Compound D (an anticonvulsant), and naproxen. The following surface stabilizers, also taught by Liversidge, were utilized: PVP, SLS, and DOSS. In addition, dissolution results utilizing the surface stabilizer hydroxypropyl cellulose (HPC) are described. *See* ¶ 11 of the Jain Declaration.

In particular, Applicants note that the Jain declaration demonstrates that solid dose forms of nanoparticulate dispersions of Danazol and PVP, described in Examples 1-5 of Liversidge, do not exhibit controlled release properties. *See* ¶ 14-21 of the Jain Declaration.

The data described in the Jain declaration below show that irregardless of the active agent, solid dosage forms of nanoparticulate active agents exhibit rapid release. In the absence of the additional structural element claimed by Applicants (matrix or coating of a rate-controlling polymer), controlled release of the component active agent over a period of about 2 to about 24 hours will not be obtained. *See* ¶ 12 of the Jain Declaration.

Moreover, data described in the Jain declaration also demonstrate that the presence of conventional excipients used in solid dose forms of pharmaceutical active agents does not result in controlled release of the component nanoparticulate active agent. Such excipients are frequently used, but not required, to optimize a commercial formulation. *See* ¶ 13 of the Jain Declaration.

The data presented in the Jain declaration demonstrates that the *structure* of a composition comprising a nanoparticulate active agent, in *combination* with a rate-controlling polymer, provides controlled release. The mere presence of a rate-controlling polymer in the absence of such a structure will not provide controlled release of the nanoparticulate active agent. Thus, a polymer that is merely associated with the surface of an active agent to maintain a particle size (*i.e.*, functioning as a surface stabilizer), such as disclosed by Liversidge, will not have a rate-controlling effect.

As Liversidge does not teach or suggest Applicants' claimed invention, withdrawal of this ground for rejection is respectfully requested.

B. Rejection of the Claims Over Liversidge in View of Vernon or Chang

In the Advisory Action mailed on August 13, 2003, the Examiner maintained the rejection of claims 1-22 and 25-53 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liversidge in view of WO 95/22318 to Vernon ("Vernon") or U.S. Patent No. 5,188,755 to Chang et al. ("Chang"). Applicants respectfully traverse this ground for rejection.

Vernon and Chang are cited by the Examiner as teaching specific rate controlling polymers. This teaching does not overcome the deficiency of Liversidge, as given the teachings of Liversidge, Vernon, and Chang, one of skill in the art at the time the claimed invention was made would not have been motivated to combine the nanoparticulate active agent compositions of Liversidge with the rate controlling polymers of Vernon or Chang. Moreover, one of skill in the art at the time the claimed invention was made would not have had a reasonable expectation of success in obtaining the claimed invention, given the teachings of Liversidge and Vernon or Chang.

IV. Conclusion

Applicants courteously request formal examination of this application in view of the above amendments and remarks. This application is now in condition for allowance, and early notice to that effect is respectfully solicited.

If any fees are due in connection with the filing of this Preliminary Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Date: Jan 5, 2004

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Beclomethasone (Nasal)

WARNINGS

The replacement of a systemic corticosteroid with beclomethasone dipropionate nasal inhaler or spray can be accompanied by signs of adrenal insufficiency.

Careful attention must be given when patients previously treated for prolonged periods with systemic corticosteroids are transferred to beclomethasone dipropionate nasal inhaler or spray. This is particularly important in those patients who have associated asthma or other clinical conditions where too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Studies have shown that combined administration of alternate-day prednisone systemic treatment and orally inhaled beclomethasone dipropionate increases the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, nasal forms of beclomethasone dipropionate should be used with caution in patients already on alternate day prednisone regimens for any disease.

If recommended doses of intranasal beclomethasone are exceeded or if individuals are particularly sensitive or predisposed by virtue of recent systemic steroid therapy, symptoms of hypercorticism may occur, including very rare cases of menstrual irregularities, acneform lesions, cataracts, and cushingoid features. If such changes occur, this drug should be discontinued slowly consistent with accepted procedures for discontinuing oral steroid therapy.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in nonimmune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure of these infectious agents. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk of developing a more severe infection is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscualr immunoglobulin (IG), may be indicated. (See the respective product information for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

During withdrawal from oral steroids, some patients may experience symptoms of withdrawal (*e.g.,* joint and/or muscular pain, lassitude, and depression).

Rarely, immediate hypersensitivity reactions may occur after the intranasal administration of beclomethasone (see **ADVERSE REACTIONS**).

Rare instances of nasal septum perforation have been spontaneously reported.

Rare instances of wheezing, cataracts, glaucoma, and increased intraocular pressure have been reported following the intranasal application of beclamthasone.

In clinical studies with beclomethasone dipropionate administered intranasally, the development of localized infections of the nose and pharynx with Candida albicans has occurred only rarely. When such an infection develops, it may require treatment with appropriate local therapy or discontinued use of treatment.

If persistent nasopharyngeal irritation occurs, it may be an indication for stopping beclomethasone dipropionate administered intranasally.

Beclomethasone dipropionate is absorbed into the circulation. Use of excessive doses may suppress HPA function.

This drug should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated fungal, bacterial, or systemic viral infections; or ocular herpes simplex.

For intranasal forms of beclomethasone dipropionate to be effective in the treatment of nasal polyps, the aerosol or spray must be able to enter the nose. Therefore, treatment of nasal polyps with beclomethasone dipropionate should be considered adjunctive therapy to surgical removal and/or the use of other medications which will permit effective penetration of this drug into the nose. Nasal polyps may recur after any form of treatment.

As with any long-term treatment, patients using intranasal beclomethasone dipropionate over several months or longer should be examined periodically for possible changes in the nasal mucosa.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma should not use a nasal corticosteroid until healing has occurred.

Although systemic effects have been minimal with recommended doses, this potential increases with excessive doses. Therefore, larger than recommended doses should be avoided.

Information for the Patient

See **PATIENT INFORMATION** section.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment by the inhalation route.

Pregnancy Category C

Teratogenic Effects: Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately 10 times the human dose. In these studies beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at 10 times the human dose or orally at 1000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when beclomethasone dipropionate nasal spray is administered to a nursing woman.

Pediatric Use

Nasal Spray: The safety and effectiveness of beclomethasone

dipropionate nasal spray have been established in children aged 6 years and above through evidence from extensive clinical use in adult and pediatric patients. The safety and effectiveness of beclomethasone dipropionate nasal spray in children below 6 years of age have not been established.

Glucocorticoids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any glucocorticoid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of glucocorticoids should be considered.

Nasal Inhalation: Safety and effectiveness in children below 6 years of age have not been established.

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WARNINGS

No information provided.

PRECAUTIONS

General

Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid (with fluticasone propionate ointment; steroid for fluticasone propionate cream). Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing

information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see

PRECAUTIONS

, **Pediatric Use**).

If irritation develops, fluticasone propionate cream or ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of fluticasone propionate cream or ointment should be discontinued until the infection has been adequately controlled.

Fluticasone propionate cream and ointment should not be used in the presence of preexisting skin atrophy and should not be used where the infection is present at the treatment site. Fluticasone propionate cream and ointment should not be used in the treatment of rosacea and perioral dermatitis.

Cream: Fluticasone propionate cream, 0.05% caused depression of A.M. plasma cortisol levels in one of six adult patients when used daily for 7 days in patients with psoriasis or eczema involving at least 30% of the body surface. After 2 days of treatment, this patient developed a 60% decrease from pretreatment values in the A.M. plasma cortisol level.

There was some evidence of corresponding decrease in 24-hour urinary free cortisol levels. The A.M. plasma cortisol level remained slightly depressed for 48 hours but recovered by day 6 of treatment.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in two of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for 1 of the 2 subjects, demonstrated a normally responsive HPA axis (see

PRECAUTIONS

, **Pediatric Use**). Fluticasone propionate cream, 0.05% may cause local cutaneous adverse reactions (see **ADVERSE REACTIONS**).

Ointment: Fluticasone propionate ointment, 0.05% (a concentration 10 times that of fluticasone propionate ointment, 0.005%) suppressed 24-hour urinary free cortisol levels in two of six patients when used at a dose of 30 g/day for a week in patients with psoriasis or atopic eczema. In a second study, fluticasone propionate ointment, 0.05% caused depression of A.M. plasma cortisol levels in three of 12 normal volunteers when applied at doses of 50 g/day for 21 days. Morning

plasma levels returned to normal levels within the first week upon discontinuation of fluticasone propionate. In this study there was no corresponding decrease in 24-hour urinary free cortisol levels.

Inf rmati n f r the Patient

Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.

4. Patients should report to their physician any signs of local adverse reactions.

Additional Information for Cream Only:

5. Parents of pediatric patients should be advised not to use this medication in the treatment of diaper dermatitis. Fluticasone propionate cream should not be applied in the diaper areas as diapers or plastic pants may constitute occlusive dressing (see **DOSAGE AND ADMINISTRATION**).

6. This medication should not be used on the face, underarms, or groin areas unless directed by a physician.

7. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests

The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test.

A.M. plasma cortisol test.

Urinary free cortisol test.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study.

Fluticasone propionate was not mutagenic in the standard Ames test, E. coli fluctuation test, S. cerevisiae gene conversion test, or Chinese

Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 mcg/kg per day and to males at up to 100 mcg/kg per day (later reduced to 50 mcg/kg per day) had no effect upon mating performance or fertility. In fluticasone propionate cream, 0.05%, these doses are approximately 15 and 30 times, and in fluticasone propionate ointment, 0.005%, these doses are approximately 150 and 300 times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate cream, 0.05% and fluticasone propionate ointment, 0.005%, assuming human percutaneous absorption of approximately 3% and the use in a 70-kg person of 15 g/day.

Pregnancy, Teratogenic Effects, Pregnancy Category C

Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse demonstrated fluticasone propionate to be teratogenic (cleft palate) when administered subcutaneously in doses of 45 mcg/kg per day and 150 mcg/kg per day. This dose is approximately 14 and 45 times, respectively, the human topical dose of fluticasone propionate cream, 0.05% and is approximately 140 and 450 times, respectively, the human topical dose of fluticasone propionate ointment, 0.005%. There are no adequate and well-controlled studies in pregnant women. Fluticasone propionate cream, and ointment, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when fluticasone propionate cream, or ointment, is administered to a nursing woman.

Pediatric Use

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Cream

Fluticasone propionate cream may be used with caution in pediatric patients as young as 3 months of age. The safety and efficacy of drug use for longer than 4 weeks in this population have not been established. The safety and efficacy of fluticasone propionate cream in

pediatric patients below 3 months of age have not been established.

Fluticasone propionate cream, 0.05%, caused HPA axis suppression in two of 43 pediatric patients, ages 2 and 5 years old, who were treated for 4 weeks covering at least 35% of the body surface area. Follow-up testing 12 days after treatment discontinuation, available for one of the two subjects, demonstrated a normally responsive HPA axis (see **ADVERSE REACTIONS**). Adverse effects including striae have been reported with use of topical corticosteroids in pediatric patients.

Ointment

Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in pediatric patients.

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